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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,362	04/23/2001	Kazuma Tomizuka	081356/0158	4670

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,362	TOMIZUKA ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-83,85 and 93-143* is/are pending in the application.

4a) Of the above claim(s) *26-83 and 85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *93-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment, filed 9/23/04, has been entered.

Claims 26-83, 85, 93-143 are pending. Claims 26-83 and 85 are withdrawn from further consideration as being directed to non-elected groups, Applicant timely traversed the restriction (election) requirement in Paper No. 8. Claims 93-143 are under current examination.

Claim Objections

The prior objection of claims 93 and 113 is withdrawn in view of Applicants' amendment to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 93-126 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention consists of a recombinant chromosome comprising the centromere of human chromosome #14, two telomere sequences, at least one recognition sequence for a site-directed recombination enzyme, at least two chromosome fragments that had not been adjacently located in a natural chromosome or in a naturally occurring chromosome fragment; and a marker gene, wherein the recognition sequence for a site-directed recombination enzyme is located between the two chromosome fragments.

In the prior Office action, the Examiner invited Applicants to point to specific page and line number to provide evidence that the production of SC20, W23 fragments and the 6-1 clone can be made by a repeatable process [see pp. 4-5 of the prior Office action, mailed 3/23/04]. In the most recent response, Applicants point to the specification for support that there are other methods of fragmenting a chromosome, such as deletion, translocation, substitution, and the like. (see p. 20, 1st full ¶) and further point to Examples 87-111 for support to show site directed cleavage of chromosomes.

These arguments are not found to be persuasive. It is maintained that the fragments (SC20, W23 and 6-1 clone) are essential to the claimed invention and the specification has not provided a repeatable method. For example, Applicants point to p. 65, part c, which recites the modification of the SC20 fragment. The SC20 fragment is, as noted previously, produced by spontaneous fragmentation of human chromosome 14. Furthermore, the examples to which Applicants point to are

directed to the truncation or cleavage of fragments which were originally generated by the spontaneous fragmentation of various human chromosomes. The various examples refer to Figure 58, which is the schematic to generate the specific chromosomes of the specification. It is noted that the fragments (SC20, W23 and 6-1 clone) are required for the generation of the resulting chromosomes. It is reiterated that these clones are essential to the claimed invention and that they are not obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public.

If the deposit is to be made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the SC20, W23 fragments and the 6-1 clone have been deposited under the Budapest Treaty and that the SC20, W23 fragments and the 6-1 clone will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

It the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,

(d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807);

and,

(e) the deposit will be replaced if it should ever become inviable.

Once the deposit has been perfected, the claims will be limited to the SC20 and W23 fragments and the 6-1 clone.

The specification teaches that it was previously thought that human chromosomes introduced into mice could not be transmitted to the mouse's progeny because of the presence of an abnormal chromosome. However, the specification teaches that a particular fragment, SC20, of the human chromosome which is used in the examples in the specification can be transmitted to progeny. The specification further teaches that there a need in the art to develop techniques that

enable the cleaving of human chromosomes at particular points, and not randomly. See pp. 62-63 of the instant specification. The specification further teaches the isolation of chromosome 2 and 22 fragments (W23 and fragment from the 6-1 clone, respectively) which are then used in combination with the SC20 fragment to produce a recombinant chromosome which is capable of producing human antibodies. The specification teaches that the fragments encoding the SC20, W23 and 6-1 clone are produced by microcell-mediated fusion, the subsequent irradiation and then isolation of the fragments. These methods clearly produce the fragments by spontaneous fragmentation.

Applicants argue that the specification fails to provide guidance with regard to the generation of recombinant chromosomes that have any two chromosomal fragments which do not encode the antibody loci, such that one of skill in the art would know how to use such a recombinant chromosome. Applicants argue that they revert to pertinent language of claims 93 and 113, which require the recombinant chromosomes to comprise at least two chromosome fragments that had not been adjacently located in a natural chromosome or in a naturally occurring chromosome fragment, and that there is no functional mandate imposed on the recited chromosome fragments that they function together. Thus, Applicants conclude that it is entirely feasible to carry, on the same recombinant chromosome, at least two chromosome fragments that encode different, unrelated genes. Further, Applicants argue that the instant application is replete with examples and

experimental techniques to make the recombinant chromosomes, and that the teachings related to "useful genes" would govern any decision the skilled artisan may make about combining chromosome fragments. See p. 24 of the Response. See pp. 23-24 of the Response.

This is not found to be persuasive. Although it may be possible for a recombinant chromosome to carry, on the same recombinant chromosome, at least two chromosome fragments that encode different and unrelated genes, the specification fails to provide any teachings as to how one of skill in the art would use such a chromosome. The specification Thus, it is maintained that the breadth of the claims is not enabling because the specification fails to provide sufficient teachings or guidance with regard to other chromosome fragments, other than the exemplified chromosome #2 and #22 fragments, which comprises a human antibody light-chain kappa gene locus, and a human light chain λ gene locus, respectively. The specification teaches that the recombinant chromosomes of the instant invention would be used to produce mice with human genes, particularly, human genes that encode for antibodies. See p. 5, for example. However, the specification fails to provide guidance with regard to the generation of recombinant chromosomes that have any two chromosomal fragments which do not encode antibody gene loci, and one of skill in the art would not know how to use such a recombinant chromosome. The breadth of the claim encompasses combinations of two proteins which do not function together, for example, an antibody locus and the amylase

locus. Further embodiments of the claims limit the chromosome 14 fragment SC20 to a centromere-comprising portion and a *fragment of a chromosome other than human chromosome 14* [see claim 106, for example]. Note that SC20 is taught by the instant specification to contain the human antibody heavy-chain locus and the chromosome 14 centromere. [See Example 68].

Applicants argue that the instant specification provides enablement for the claimed invention because Applicants have provided detailed technical guidance and numerous working examples to show in precise detail as to how to make and use the presently claimed invention. Applicants argue that they teach how to perform a telomere-directed truncation of a chromosome and how to recombine or translocate the resultant chromosome fragment with other genetic material. See p. 22 of the Response. Applicants further argue that undue expermination is not a single, simple factual determination, but a conclusion reached by weighing all factual consideration. Applicants argue that they have shown how to construct a recombinant chromosome with three different chromosomal fragments, and it is not necessary to provide evidence for each embodiment of their invention. Further, Applicants have provided a written description for chromosome 21 and an enabling disclosure for manipulating chromosomal fragments to practice the claimed invention.

This is not found to be persuasive. In particular, the specification provides teachings with regard to specific fragments, and methods of truncating and using

these specific fragments to produce other fragments. Thus, the specification only provides sufficient enabling guidance for the above-recited chromosome fragments (SC20, W23 and 6-1 clone). The state of the art of artificial chromosomes is such that one of skill in the art would not know how to use a recombinant chromosome that contained the SC20 fragment and any particular other chromosome fragment, other than the exemplified W23 and fragment from the 6-1 clone because the specification fails to provide guidance for such recombinant chromosomes because the specification teaches that these fragments are produced by spontaneous fragmentation of chromosomes.

Accordingly, in view of the lack of teachings or guidance provided by the specification with regard to the production of recombinant chromosomes have any two chromosome fragments, other than the exemplified chromosome 14, 2 and 22 fragments [SC20, W23 and fragment 6-1 clone], it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Claims 127-143 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that the claims meet the written description requirement, and point to page 66, line 20-page 67 line of the specification for support. This is not found to be persuasive. Applicants argue that argue that specification provides sufficient for a specific description of the chromosome 21 fragment. It is noted that the chromosomal 21 fragment in the instant specification is produced by spontaneous fragmentation. Thus, merely pointed to the specification to show that mice retain this fragment fails to provide it with sufficient written description. That is, one of skill could not envision the sequence of the claimed fragment, and the detailed chemical structure of the chromosome fragment and how to use it as instantly claimed. Thus, it is maintained that the specification fails to provide a specific description of the chromosome 21 fragment.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claims 127-143 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification teaches the spontaneous generation of a human chromosome 21 fragment screened from a monochromosomal hybrid cell library that was stable in a chimeric mouse, and thus, this fragment could be used in the methods taught by the specification for the SC20 (chromosome 14) fragment. See pp. 66-67, bridging ¶. This is not found to be enabling because the state of the art of producing artificial chromosome is such that without specific guidance provided by the specification, one of skill in the art would not be able to make a chromosome 21 fragment comprising a centromere, recombinant chromosomes comprising this fragment and methods of making the same. This is because the state of the art of generation artificial chromosomes is unpredictable, and relies on spontaneous fragmentation of chromosomes to identify desired chromosome fragments. This is supported by the instant specification which teaches that there a need in the art to develop techniques that enable the cleaving of human chromosomes at particular points, and not randomly. See pp. 62-63 of the instant specification. However, the specification fails to provide specific teachings with regard to the generation of the claimed chromosome 21 fragment, wherein the fragment has a centromere, and one of skill in the art would not be able to rely upon the teachings of the art for the generation of a particular fragment, as claimed. For example, the specification fails

to provide teachings or guidance with regard to the particular isolation of the fragment, the sequence of the claimed fragment or methods of how such a fragment would be produced, or working examples with regard to chimeric mice comprising this fragment, or guidance, teachings or evidence that such a fragment would contain a centromere sequence, as required by the claims. The specification merely suggests that such a fragment exists, but does not teach the specific production of the fragment, and one of skill in the art would not be able to rely upon the state of the art of artificial chromosome engineering, because the art relies upon methodologies that produce random fragments of chromosomes.

Accordingly, in view of the lack of teachings or specific guidance by the specification with regard to the production and use of the claimed recombinant chromosome comprising a chromosome 21 fragment, wherein the chromosome fragment has a centromere, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejections of claims 93, 94, 95, 98 101 and 113are withdrawn in view of Applicants' arguments or amendment to the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 93 is rejected under 35 U.S.C. 102(b) as being anticipated by Tomizuka *et al.* [Nat. Gen., 16:133-143, 1997, cited in prior Office actions].

Applicants note that the Examiner withdrew the prior rejection on Oct. 23, 2002. It is noted that upon further consideration, the rejection is reinstated and proper. Applicants argue that Tomizuka do not teach the claimed invention because the presently claimed chromosome requires the presence of at least two distinct chromosomal fragments, and these two fragments are selected for inclusion in the recombinant chromosome on the basis that nether fragment existed next to the other in their unfragmented state. Thus, the claim requires the bringing together of at least two distinct and previously unconnected chromosome fragments in the claimed recombinant chromosome. Applicants argue that Tomizuka's intact chromosome does not anticipate the claimed invention because it does not involve fragmented chromosomes and does not result in a composition that comprises these discreet structural elements. See p. 29 of the Response.

This is not found to be persuasive. The claim does not require, as Applicants argue, that the fragments are selected on the basis that neither existed next to the other in their unfragmented state. The claims recite that the fragments had not been adjacently located in the a natural chromosome. That is, the two chromosome fragments that were distal prior to the insertion of loxP would remain distal, that thus, not be adjacent to each other. There is no recitation or requirement in the claim that the two fragments be from different chromosomes, for example.

Applicants argue that claim 93 requires the recombinant chromosome to possess co-joined chromosomal fragments, and that the placement of a recognition site, in Tomizuka, does not implicate co-joined framgnets, as prescribed. Applicants further argue that the claim recites a recognition site between the aforementioned fragments, and does not pertain to a site that is situated with a single chromosome or chromosome fragment. See p. 30 of the Response.

This is not persuasive. Firstly, the claims do not require that the recognition sequence be between the two fragments. The claim does not require a specific sequential order. Thus, Tomizuka's teaching of a recognition site for a site-directed recombination enzyme (loxP) is sufficient to meet the claimed limitation. Furthermore, there is nothing in the claims that require the fragments to be from different chromosomes, or co-joined. The chromosomes as taught by Tomizuka, anticipate the claimed invention because the anticipate each element of the claim.

The chromosome fragments are not adjacent to each other in the naturally occurring chromosome, nor in the resulting recombinant chromosome.

Tomizuka teach the introduction of human chromosome or chromosome fragments into mouse ES cells by microcell-mediated chromosome transfer [MMCT]. In particular, Tomizuka teach the introduction of chromosomes (or chromosome derived fragments) which carry the genes for human antibodies from unrearranged human Ig genes [Ig heavy, λ or κ genes], which are found on human chromosomes 2, 14 and 22, into mouse ES cells. In particular, whole cell fusion of human primary fibroblasts with mouse A9 ES cells was performed, and the resulting hybrid cells were screened by PCR and FISH [see p. 133-134 and Figure 1]. Cells were selected by G418 or puromycin drug resistance [see p. 134, col 1-2, bridging paragraph]. It was found that intact human chromosomes 14 and 22 were identified in hybrids A9/14-C11 and A9/22-G2. Tomizuka teach using the Cre-loxP system to replace specific mouse chromosomal regions with the corresponding human chromosomal fragment in the microcell-hybrid ES cells by homologous recombination [see p. 140, 2nd column, 2nd full paragraph, lines 4-7].

Accordingly, Tomizuka *et al.* anticipate the claimed invention.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

tnt
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